



NOTES RETROVIRUSES

MICROBE OVERVIEW

- RNA viruses
 - Require DNA generation, integration into host DNA → produce viral progeny
- Large viral family
 - Seven genera
- Target cells determined by viral glycoprotein spikes on cell membrane → recognized cell surface receptors, coreceptors → viral entry → provirus creation
 - Viral reverse transcriptase takes single-stranded viral RNA genome → creates linear, double-stranded DNA virus → provirus
- Provirus integration (via integrase) into host-cell DNA → viral particle production
 - Integration stability of provirus, transmission to host-cell progeny determines retroviral infection persistence in host organism
- Protein core
 - Two linear, $\oplus$ -sense, single-stranded RNA genomes (7–11 kb)
 - Enzymes (gene locus) needed for viral replication (protease—pol gene, p10 locus; reverse transcriptase—pol gene, p66 locus; integrase—pol gene, p32 locus)

TYPES

Human endogenous retroviruses

- Proviral DNA/partial genomic sequences integrated into host-genome
- Constitutes up to 8% of human DNA
- Vertical transmission via germline cells
- Translated DNA does not lead to infectious viruses; may → functional proteins

Human exogenous retroviruses

- Passed horizontally via exposure to blood, sexual secretions, breast milk

Morphology

- Lipid-enveloped particles 80–100nm diameter

HUMAN IMMUNODEFICIENCY VIRUS

[osms.it/HIV-\(AIDS\)](https://osms.it/HIV-(AIDS))

PATHOLOGY & CAUSES

- HIV: human immunodeficiency virus
- Member disease of *Lentivirus* genus of *Retroviridae* family
 - Characterized by immune cell targeting, immunodeficiency

Two pathogenicity targets

- Immune system
 - Mucosal HIV virion infiltration → bloodstream spread → infection of T cells, dendritic cells, macrophages → latency (may be chronic, indolent) → active replication → symptom progression/emergence → further replication → severe

VISIT...

LANZAROTE
Caliente.COM

immunocompromise, progression to AIDS (acquired immune deficiency syndrome)

- HIV infection → targeting, infection of CD4+ cells (e.g. CD4+ T-lymphocytes, monocytes, macrophage) → replication, spread → ↓ CD4+ cells → immunodeficiency
- Co-receptor CCR5 important in early infection; persistence
- Central nervous system (CNS)
 - HIV infection → macrophage/microglia infection → abnormal CNS cytokine milieu → neuronal cell death

Structure

- 110nm diameter spherical virion
- Core surrounded by lipid bilayer envelope
- Lipid envelope
 - External glycoprotein gp-120, anchored by gp-41
 - Binding sites for host-cell CD4+ receptor (co-receptors—chemokine receptors; especially CCR5, CXCR4)
- Core
 - Two single-stranded RNA copies
 - Two transfer RNA primers (host-cell origin)
 - Multiple enzyme copies: reverse-transcriptase (RT), integrase, ribonuclease H (RNase H)
 - Other proteins: vpr, vif, nef (important in early virion life-cycle)

Genome

- 9kb
- Similar to other retroviruses (six genes—tat, rev, vpr, vpu, vif, nef)
 - HIV-2 specific: Vpx gene (homologous to gene in simian immunodeficiency virus (SIV); not present in other lentiviruses)

Life cycle

- Cell contact, fusion: gp-120, CD4+ receptor fusion → gp-120 conformational change → opened gp-120 recognition site → gp-120 binding to host-cell co-receptor (CCR5/CXCR4) → gp-41 conformational change → gp-41 hydrophobic domain exposed → virion lipid bilayer insertion into cell membrane → virus-host-cell membrane

fusion → viral entry

- Viral genome replication: viral RNA transcribed by viral RT in host-cell cytoplasm → HIV provirus production (double-stranded complementary DNA transcript) → transport to nucleus → integrase insertion in cell DNA → viral DNA transcription → viral RNA, protein
 - Host-cell activation (naïve T cells) important factor in determining active vs. latent HIV replication
 - Antigen/cytokine-mediated T cell activation → NF-κB (nuclear transcription factor) cell stress activation → ↑ NF-κB promoter-associated gene transcription (in HIV proviral DNA) → ↑ viral replication → viral RNA, protein aggregation in cytoplasm → viral protein cleavage (e.g. gag) → viral content assembly → ↑ virion production (↑ virion budding → cell death)
- Host-cell death: ↑ virion budding → ↑ host-cell plasma membrane permeability; ↑ viral replication → native protein synthesis interference → dysregulated cellular protein concentrations → cell death
 - Non-cytopathic host-cell HIV infection: HIV infection → inflammasome pathway activation → pyroptosis (inflammatory cytokine, cellular content release) → immune cell recruitment → viral spread (likely plays large role in HIV infection spread)

Transmission

- HIV-1, HIV-2
- Three transmission modes
 - Sexual: USA—biologically-male individuals engaging in same-sex sexual contact (MSM) particularly important transmission mode (highest disease incidence → homosexual biologically-male individuals); global—majority of sexual transmission via heterosexual intercourse; co-existent sexually-transmitted disease (genital ulceration especially) → ↑ transmission risk during intercourse
 - Parenteral: non-iatrogenic, intravenous (IV) drug users (shared needles, syringes, other paraphernalia contaminated with HIV ⊕ blood); iatrogenic (hemophiliacs who received

HIV-contaminated factor VII, IX concentrates; HIV-contaminated blood transfusion recipients; health personnel—e.g. needle-stick injuries)

- **Vertical, mother-to-infant:** in utero, transplacental spread; infected birth canal → delivery → neonatal infection; neonatal HIV ⊕ breast milk ingestion
- HIV-2 only
 - Believed to be zoonosis resulting from SIV cross-speciation infection
 - Endemic areas correlate with those of sooty mangabey
 - Less transmissible than HIV-1

Disease

- Acute retroviral syndrome
- AIDS

TYPES

- Likely related to SIV
- Two human virus types
 - HIV-1, HIV-2

RISK FACTORS

- West Africa residence (HIV-2), homosexual/bisexual biologically-male individuals (USA), IV drug users, hemophiliacs, blood (or component) transfusion recipients, maternal HIV infection

COMPLICATIONS

- Opportunistic infections, secondary malignancies, AIDS, neuropsychiatric disease

SIGNS & SYMPTOMS

Acute retroviral syndrome

- Self-resolving, flu-like syndrome; sore throat; myalgias; fever; weight loss; fatigue

Chronic infection

- Variable
 - Asymptomatic → minor infection
 - Oral/vaginal candidiasis, herpes zoster, mycobacterial tuberculosis (especially Sub-Saharan Africa)

AIDS

- Persistent fever (> one week); fatigue; weight loss; diarrhea; generalized lymphadenopathy (LAD); serious, opportunistic infection
- Secondary neoplasms
- Neuropsychiatric disease
 - Delirium; major depression; mania; schizophrenia; post traumatic stress disorder; substance abuse, addiction (commonly HIV infection risk factor)
 - **Dementia** (AKA AIDS dementia complex): cytomegalovirus encephalitis, progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, cryptococcal meningitis, CNS lymphoma

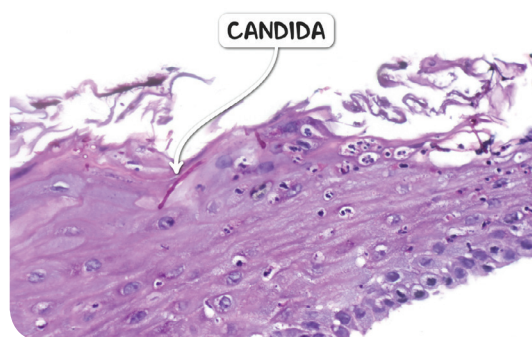


Figure 93.1 An esophageal biopsy composed of squamous mucosa with candida hyphae. Esophageal candidiasis is a common opportunistic infection in individual with AIDS.

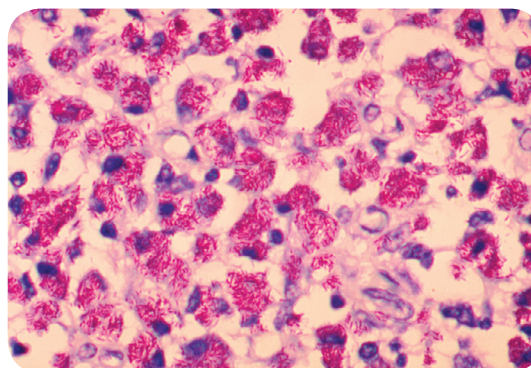


Figure 93.2 The histological appearance of mycobacterium avium intracellulare. There are numerous organisms within the cell cytoplasm.

NATURAL HISTORY OF HIV INFECTION

DISEASE PROGRESSION	CELLS INVOLVED	CLINICAL MANIFESTATION	KEY FACTS
MUCOSAL INFECTION	Mucosal memory CD4 ⁺ T cells, macrophage, dendritic cells	Asymptomatic	Important component: host-cell CCR5 co-receptor ↑ infection likelihood with disrupted mucosa (e.g. ulcerative STDs)
LYMPHOID TISSUE INVOLVEMENT	Dendritic cells (membrane-bound virion)	Asymptomatic; may mimic acute retroviral syndrome symptoms depending on viremic load	Important component: FcR-binding of antibody-virion complex Opsonized virion still capable of CD4 ⁺ T cell infection in lymph nodes; cell-to-cell contact important for viral spread
VIREMIA	Circulating CD4 ⁺ T cells, macrophage	Acute retroviral syndrome	Steady-state viremic HIV RNA load predictive of CD4 ⁺ cell decline, disease progression
IMMUNE RESPONSE	Serum CD8 ⁺ , HIV-specific T cells	N/A	Effectiveness HLA-dependent
LATENCY	CD4 ⁺ T cells	Asymptomatic/minor, opportunistic infections (e.g. oral candidiasis, herpes zoster)	Integrated viral DNA dormant (host-cell does not transcribe) Viral mutation may occur (e.g. change in co-receptor preference)
ACTIVE REPLICATION	CD4 ⁺ T cells	Viral load-dependent	DNA provirus translation, transcription → ↑ virion production → ↑ virion budding Trigger: cytokine/microbial infection → NF-KB activation → HIV proviral promoter activation, translation
AIDS	CD4 ⁺ T cells	Opportunistic infections (local and disseminated), secondary neoplasms	↑↑ HIV viremia, ↓↓ host defense → severe immunocompromise Variable progression rate from acute infection to severe immunocompromise (likely HLA-dependent)

STD - sexually transmitted disease, AIDS - acquired immunodeficiency syndrome

OPPORTUNISTIC INFECTIONS IN HIV/AIDS

	ORGANISM	CLINICAL DISEASE
PROTOZOAL/HELMINTHIC	<i>Cryptosporidium/Isosporidium</i>	Enteritis
	<i>Pneumocystis jiroveci</i>	Pneumonia; disseminated infection
	<i>Toxoplasma gondii</i>	Pneumonia; CNS infection
FUNGAL	<i>Candida albicans</i>	Esophageal; tracheal; pulmonary; invasive (indwelling catheter individuals)
	<i>Cryptococcus neoformans</i>	CNS infection
	<i>Coccidioides</i>	Disseminated disease
	<i>Histoplasma capsulatum</i>	Disseminated disease
BACTERIAL	<i>Mycobacteriosis (M. avium-intracellulare, M. tuberculosis)</i>	Avium-intracellulare: extrapulmonary, disseminated disease
	<i>Nocardia asteroides</i>	Tuberculosis: pulmonary/extrapulmonary
	<i>Salmonella typhi</i>	Pulmonary, intestinal, retinal, CNS infection
VIRAL	Cytomegalovirus	Pulmonary, intestinal, retinal, CNS infection
	Herpes simplex	Localized/disseminated disease
	Varicella-zoster	Localized/disseminated
	JC	Progressive multifocal leukoencephalopathy

CNS - central nervous system

SECONDARY HIV INFECTION NEOPLASMS

	CAUSATIVE ORGANISM	CLINICAL MANIFESTATION
KAPOSI SARCOMA	Human herpesvirus 8	Widespread, tumor burden of skin, mucus membranes, GI tract, lymph nodes, lungs
LYMPHOMA (B CELL, HODGKIN TYPE)	Epstein-Barr virus	Painless, regional LAD
CERVICAL, ANAL CARCINOMA	Human papillomavirus	Presence/abnormal bleeding at neoplasm site

DIAGNOSIS

LAB RESULTS

- ⊕ Viral RNA level test (> 100,000 copies/mL)
 - May be used in indeterminate HIV-1/HIV-2/ p24 immunoassay
- Leukopenia
 - ↓↓ CD4+ count
 - CD4+:CD8 ratio < 1

Serology: enzyme-linked immunoassay (ELISA)

- IgG, IgM, p24 antibody testing
 - Time to positivity: 15–45 days (P24 (viral core protein) earliest positive marker)
 - May be combined for HIV-1, HIV-2, p24 immunoassay in diagnostic, screening purposes

OTHER DIAGNOSTICS

- Flu-like illness
- Opportunistic infection
- Needlestick injury with HIV ⊕ individual
- Unprotected sex with partner of unknown/ HIV ⊕ status

TREATMENT

MEDICATIONS

Highly active antiretroviral therapy (HAART)

- Antiretroviral drug combination regimen
 - Early initiation → ↓ morbidity, ↓ mortality, ↓ transmission risk (regardless of CD4+ count)
- Six distinct drug classes
 - Combination of three drug types used for effective viral load management, combat particular drug class resistance development
- Protease inhibitor preferred initial agent
 - Resistance testing results → narrow therapy
- Complications
 - Immune reconstitution inflammatory syndrome
 - ↓ in clinical state (symptom return experienced during active viremic phase), despite ↑ CD4+ levels
 - Believed to be due to reinvigorated host response to high antigenic burden of persistent microbes, remaining viral load

Pre-exposure prophylaxis

- Daily tenofovir use can very effectively ↓ transmission

HIV ANTIRETROVIRAL THERAPIES (ART)

	DRUG TYPE	MECHANISM OF ACTION	SIDE EFFECTS	KEY FACTS
ENTRY INHIBITORS	CCR5 inhibitors - maraviroc Fusion inhibitors - enfuvirtide	CCR5 inhibitors interfere with viral gp-120, host-cell membrane fusion Fusion inhibitors prevent viral gp-41, host-cell membrane co-binding	Hepatic dysfunction (especially with creatinine clearance < 30 mL/min)	N/A
NRTIs	Adenosine analogue - tenofovir Cytosine - Emtricitabine, lamivudine Guanosine - abacavir zidovudine	Nucleotide-specific agents that undergo phosphorylation → triphosphate residue → steric inhibition of viral RT → ↓ provirus DNA transcription	Mitochondrial toxicity - peripheral neuropathy, pancreatitis, lipoatrophy, hepatic steatosis; Tenofovir - kidney injury Abacavir - contraindicated in HLA-B*5701 due to HSN	Resistance emerges quickly; two nucleotide analogues are usually combined
NON-NRTIs	Second generation - rilpivirine + etravirine	Bind hydrophobic pocket near polymerase active site → steric change → ↓ ability for naturally-occurring nucleosides to bind active site	Rash, QT prolongation, neurologic, psychiatric side effects	Not active against HIV-2
INTEGRASE STRAND TRANSFER INHIBITORS	Raltegravir, elvitegravir, dolutegravir	Inhibit preintegration complex binding → strand transfer interference → DNA integration termination	Insomnia, dizziness	Preferred third agent in drug-naïve individuals
PROTEASE INHIBITORS	Darunavir, atazanavir Boosting agent - ritonavir, cobicistat	Inhibit gag-pol polyprotein cleavage → dysfunctional viral maturation → immature virion production	Insulin resistance, hyperglycemia, diabetes, hyperlipidemia, lipodystrophy, hepatotoxicity	Most drug-drug interactions occur due to boosting agents

NRTIs - nucleoside/nucleotide reverse transcriptase inhibitors, RT - reverse transcriptase

HIV OPPORTUNISTIC INFECTION PROPHYLAXIS

CD4+ COUNT (cells/microL)	ORGANISM	DISEASE	PROPHYLAXIS
ANY COUNT	<i>Mycobacterium tuberculosis</i>	Tuberculosis	N/A
< 250	<i>Coccidioides</i>	N/A	Fluconazole
< 200	<i>Pneumocystis jirovecii</i>	Pneumocystis pneumonia	Trimethoprim-sulfamethoxazole (TMP-SMX)
< 100	<i>Toxoplasma gondii</i>	Pneumonia	TMP-SMX Dapsone, pyrimethamine, leucovorin
< 50	<i>Mycobacterium avium</i>	Disseminated	Azithromycin

OTHER INTERVENTIONS

Monitoring

- HIV RNA testing two, four, eight weeks after ART initiation
 - Continue testing every two weeks until levels below detection limits
 - Drug resistance testing at 24 weeks if ↑ in RNA viral level/no ↓ in RNA levels
- Once viral suppression achieved → repeat testing for RNA levels 3–6 months

Screening

- One-time for individuals 13–75 years old
- Pregnant individuals (even in negative prior pregnancy screening)
- Annual/more frequent for high-risk individuals
 - MSM (USA)
 - IV drug users
 - Sex partners of HIV unknown status, HIV ⊕, bisexual, individuals who inject drugs
- Blood factor screening
 - Plasma/recombinant factor hemophiliac recipients

Opportunistic infection prophylaxis

- Determined by CD4+ count
- Situational avoidance advised (e.g. cat litter, *Toxoplasma* exposure)

Pre-exposure prophylaxis

- Indications
 - High-risk sexual behavior/drug use
 - Reliable individual to adhere to daily medication regimen

HUMAN T-LYMPHOTROPIC VIRUS

osms.it/human_t-lymphotropic_virus

PATHOLOGY & CAUSES

- Oncogenic retrovirus endemic to certain areas of world → T cell leukemia/lymphoma
 - AKA HTLV-1
 - Genus: Deltaretrovirus
- Structure
 - Enveloped, single-stranded RNA virus
 - Only human pathogen of oncovirus subfamily
- Genome
 - Contains retrovirus-consistent gag, pol, env, long terminal repeat (LTR)
 - HTLV-1 specific: tax; encodes protein essential for viral replication; viral RNA transcription stimulation from 5' LTR
- Transmission
 - Usually via infected T cells (vs. virion particle)
 - Breastmilk, sexual transmission, blood transfusion, tissue donation, IV drug use, zoonotic transmission (nonhuman primate source)
- Disease
 - Adult T cell leukemia/lymphoma
 - Myelopathy/tropical spastic paraparesis

Targets CD4+ cells

- Unlike HIV life cycle, pathogenesis; largely unknown targeting, infection, replication mechanisms
 - Tumor initiating cell appear to be CD4+ memory T cell with stem-cell-like properties
- Distinct from HIV
 - HTLV-1 → proliferation of T cell population rather than killing of cells

Infectious replication

- Integrated provirus re-expression → intracellular virion

- Integrated provirus → mitotic cell division → host cell replication
 - Low replication rate
 - Host cell DNA polymerase ensure high transcription fidelity (HTLV-1 genetically stable)

Tax-specific oncogenic hallmarks

- Inr pro-growth signaling, cell survival
 - Stimulates AKT (via PI3K), NF-κB, cyclin D2, ↓ CDK inhibitors → ↑ pro-survival, cell growth → polyclonal T cell expansion
- Inc genomic instability
 - Interference with DNA-repair function
 - Inhibition of cell cycle checkpoints (activated by DNA damage)

RISK FACTORS

- Travel/residence in Japan, Caribbean basin, South America, Africa
 - Sporadic incidence in USA

COMPLICATIONS

- Mycosis fungoides
 - Cutaneous T cell leukemia/lymphoma manifestation
- Uveitis
- Gastric cancer

Rheumatologic, pulmonary disorders

- Chronic inflammatory arthropathy
 - Shoulder, wrists, knees
- Sjögren syndrome
- Immune thrombocytopenia

SIGNS & SYMPTOMS

Adult T cell lymphotropic leukemia/lymphoma

- Skin lesions
- Generalized lymphadenopathy
- Hepatosplenomegaly

Myelopathy/spastic paraparesis

- Insidious-onset lower extremity weakness, spasticity
- Hyperreflexia, ankle clonus present
- ⊕ extensor plantar responses
- Lumbar pain
- Others
 - Back pain
 - Detrusor instability → nocturia, urinary frequency, incontinence
 - *Minor sensory change*: paresthesias, ↓ vibrational sense

DIAGNOSIS

DIAGNOSTIC IMAGING

- Lytic bone lesions

MRI

- Tropical spastic paraparesis
 - Cervical/thoracic cord atrophy
 - Spinal cord white matter disease

LAB RESULTS

- Leukopenia
- Hypercalcemia
- Histology is variable, with characteristic circulating tumor cells
 - Medium-sized lymphocytes with condensed chromatin, bizarre hyperlobated nuclei (AKA clover leaf/flower cells)

- ELISA
 - Antibody against HTLV-1 virus detection
- Western blot
 - Confirmatory testing for ELISA
- Polymerase chain reaction (PCR)
 - Available for HTLV-1
 - Useful with ↑↑ suspicion (ELISA negative)
- Flow cytometry
 - ↑ FoxP3 expression in leukocytes (↑ regulatory T cell-indicative)
 - Otherwise immunophenotypically mature T lymphocytes

OTHER DIAGNOSTICS

- Travel/residence in endemic area

TREATMENT

- No therapy proven to benefit affected individuals

MEDICATIONS

- Corticosteroid therapy may slow disease course
- Antiviral therapy
 - NRTI zidovudine, IFN-alpha proven beneficial

OTHER INTERVENTIONS

Prevention

- Endemic area-avoidance when breastfeeding
- Blood donor screening
- Safe-sex practices
- Discourage needle sharing